

Alternative Cancer Therapies, II

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Cold River Veterinary Center

Cold River Veterinary Center is a small animal practice with special emphasis on holistic medicine and the use of natural therapies to treat chronic degenerative diseases. CRVC offers non-toxic cancer therapies, BioMedical Profiles, homeopathic remedies, a large nutritional pharmacy, diagnostic ultrasound, high frequency radiography, electrosurgery, and intravenous vitamin and oxygen therapy. In addition to office appointments, we serve clients by mail and telephone consultation. Cold River Veterinary Center is located on Route 103, just south of Rutland, Vermont. Our address is 87 East Clarendon Road, North Clarendon, VT 05759. Telephone (802) 747-4076. Fax (802) 747-0283.

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Metastasis

Carcinogenesis is thought to arise from a toxic insult to the body, a failure of gene repair, or both.¹ The inciting cause may be a sudden, overwhelming event such as exposure to a high dose of radiation, or chronic low-level exposure to a chemical irritant. In any event, injury to the genetic material is greater than our ability to repair the damage. The injury leads to a defect in the gene, or gene function, causing uninhibited cell proliferation.

The key feature of carcinogenesis then, is a destructive event to nuclear DNA or RNA. Mitochondrial DNA is also susceptible to toxic insults, causing aberrant gene expression. Any number of genetic mutations, translocations, deletions, insertions, amplification of gene products, methylation of DNA, and other changes could dysregulate mitotic cell division and allow a tumor to grow. While DNA is the primary target of carcinogens, other macromolecules including repair enzymes and polymerases can be affected, causing mutations indirectly.

The likelihood of tumor development increases with certain nutritional, lifestyle, and environmental modifications, including:

- inefficient detoxification of carcinogens
- insufficient antioxidant vitamins, minerals, enzymes
- abnormal DNA repair mechanisms
- lack of immune recognition of malignant cells
- depressed Natural Killer and cytotoxic T-cell activity

Cancer cells have unusual morphological and growth characteristics that distinguish them from normal cells. Cancer cells lack the differentiation and organization seen in well-differentiated cells. Carcinomas, round cell tumors, and some sarcomas have a tendency to metastasize or spread to distant sites. Somehow the genetic regulatory mechanisms that govern cell division and maturation are ineffective in neoplasia.

Metastasis

Metastasis occurs when cancer cells separate from a primary site and migrate to distant sites via lymphatic or blood vessels, or across a body cavity. Metastatic disease is associated with a poor prognosis and failure of early therapeutic intervention.

Metastasis itself is not a haphazard event. Different tumor cell types have a tropism or predilection for certain tissues. We know that some tumors readily metastasize to specific organs, bypassing other tissues including endothelium, through which the tumor cells migrate. Recent research suggests that this is the result of interactions between surface-bound glycoconjugates on tumor cells, and host tissue protein receptors called *lectins* that accept them.²

Lectins

Lectins are cell-surface proteins that attract or bind the branching sugar molecules of glycoproteins and glycolipids found on tumor cells. In other words, tumor cells have glycoproteins on their cell surface that can bind to lectins expressed on specific tissues such as lung or liver parenchyma. Cell:cell interaction leads to adherence of a tumor cell, and establishment of metastasis. Metastasis is always associated with a worsening prognosis and in itself is an important obstacle to curing cancer.

Cell:cell interactions

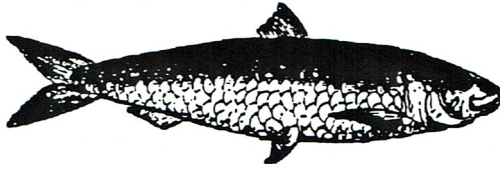
Metastasis involves many host-cell:tumor-cell interactions:

- angiogenesis
- invasion into adjacent tissue compartments
- intravasation into capillaries, venules, and lymphatics
- intravascular survival
- arrest near a favorable site
- extravasation from the vascular compartment to adjacent tissue
- adherence to different tissue
- proliferation in the distant organ

These events are mediated by cytokines, growth factors, and cell-signaling molecules. For example, transforming growth factor beta is one regulator of endothelial cell growth.³ It inhibits proliferation of endothelium or promotes expression of a more differentiated phenotype.⁴ Tumor cells however, do not respond to the inhibitory activity of growth factor beta. Basic fibroblast growth factor is a proangiogenic peptide that stimulates the migration, proliferation and protease activity of endothelial cells.⁴ Insulin-like growth factors are important stimulators of tumor cell proliferation.

Inflammation and metastasis

Chronic inflammation and production of pro-inflammatory cytokines not only serve to perpetuate tumor growth, they also increase the risk of metastatic disease. Nutritional intervention and use of natural anti-inflammatory substances can reduce tumor-associated



disease and delay or prevent metastasis.⁵ For example, the anti-inflammatory effects of θ -3 essential fatty acids found in marine fish and flax seed oil, the green tea polyphenol epigallocatechin,

the bioflavonoid curcumin from turmeric, anthocyanins from grape seed, and gum resin from *Boswellia serata* are safe, early intervention therapies that can protect the body from metastasis due to their anti-inflammatory activity.

Tumor microenvironment

The cell environment includes adjacent cells, extracellular matrix, and interstitial fluid. A tumor's response to stimulatory or inhibitory cell signals may be affected by its "cellular context" or microenvironment. Whether or not a transformed cell evolves into a macroscopic tumor is highly dependent on neighboring cells.⁶ Cancer cells by definition are wildly proliferative, and invasive. For a tumor to spread or expand, there must be a degree of permissiveness by normal cells.

Metastatic cells can release matrix-degrading *metalloproteinases* allowing a tumor to expand. These enzymes liberate paracrine growth factors such as basic fibroblast growth factor from the matrix. Basic fibroblast growth factor promotes formation of new blood vessels (angiogenesis), providing a further stimulus for tumor expansion. Down-regulation of genes that encode for angiogenic inhibitors such as thrombospondin would be permissive of new vessel formation and tumor survival.

The distribution of tumors (metastasis) is not simply due to regional anatomy. If it were, metastasized cells would arrest at the first capillary bed encountered. Tumor cell migration and establishment at a distant site appears to be related to the target organ itself. The recognition of a tumor cell for a preferred organ can be explained by a "lock and key" analogy, where cell:cell recognition is specific. Cell:cell interactions include chemotactic cytokines that help a tumor cell find the appropriate "address"; surface molecules involved in recognition or "fit"; expression of adhesion molecules to promote cell:cell contact, and production of *integrins* that promote stability of cells within the extracellular matrix.

Adhesion molecules are expressed that promote cell:cell contact, and cell:matrix contact.⁷ In autografts, transplanted tissues introduced into the wrong matrix get rejected. Cancer cells however have their own recognition and receptor molecules that impart metastatic potential. Malignant cells differ in the number and pattern of surface glycoprotein and lectin molecules compared to normal cells.⁸

There is a superfamily of cadherin adhesion molecules that inhibit cell migration out of a tissue compartment. *E-cadherin* is a cell surface glycoprotein that plays an important role in homotypic tumor cell adhesion.^{4,7} Diminished expression of E-cadherin is associated with aggressive behavior in many different human tumors. A therapeutic option for preventing metastasis might involve the promotion of E-cadherin gene expression, or simply promoting normal cell:matrix structure. Polysulfated glycosaminoglycans (PSGAGs) are known to repair connective tissue and inhibit matrix-degrading enzymes such as collagenase, elastase, and hyaluronidase. Further research is needed to determine if cartilage derivatives containing PSGAGs have a place in preventing metastasis.

Galectins

Cell:cell adhesion involves two cell surface components: 1) a carbohydrate-rich protein (glycoprotein), and 2) a carbohydrate-poor protein (lectin). Lectins and their role in cell:cell interactions have been studied in plant tissues as well.⁹ *Galectins* are cell surface proteins with an affinity for galactose, one of the saccharides conjugated or linked to surface glycoproteins on a cancer cell. Galactose-binding lectins (galectins) have been identified on cancer cells and are thought to contribute to their metastatic potential.¹⁰ These molecules have been identified in a subline of male Copenhagen inbred rats with spontaneously occurring prostate adenocarcinoma, and murine melanoma cells.

Mouse B16-F1 melanoma is frequently used to study metastasis because it is highly metastatic, and metastasizes in predictable patterns. When injected into a tail vein, B16 F1 melanoma cells consistently metastasize to the lung.¹¹ Blocking cancer-specific lectins (or organ-specific lectins) with an appropriate glycoprotein or glycoconjugate would theoretically inhibit the establishment of metastasis.¹²

Pectin

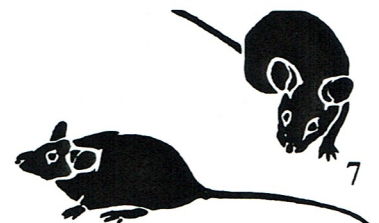
Pectin is a water-soluble plant fiber present in cell walls, where it functions as a cement, holding cells together. The main commercial source for pectin is citrus rinds and other fruits. Acid extracts of citrus pectin are used in anti-diarrheal medications (i.e., Kao-pectate), in

jams and jellies, and as a suspending agent in various pharmaceuticals. Pectin and other soluble plant fibers have a beneficial effect on intestinal flora, enhancing the growth of anaerobic and aerobic bacteria.¹³ Chemically it is a soluble carbohydrate (branched polygalacturonic acid polysaccharide) of high molecular weight. Galacturonic acid makes up the majority of a central chain with side chains of mostly D-galactose, L-arabinose, D-glucose, and D-xylose. The highly branched structure can be altered by a series of pH changes to separate the large branched pectin molecule into smaller, more linear compounds with average MW of 10,000 kDa. The resulting product is available commercially as modified citrus pectin (MCP), rich in galactose moieties.

Modified Citrus Pectin

MCP is a food supplement that resembles citrus pectin but has smaller, nonbranched carbohydrate chains of galactose. Recent studies have demonstrated that MCP delays or retards cancer metastasis by combining with galactose-specific proteins (galectins) on the cancer cell surface. Research by Inohara and Raz suggests that carbohydrate recognition by cell surface galectin is involved in cell:matrix interaction, has a role in anchorage-independent growth, and affects embolization of tumor cells in vivo.¹⁴ MCP may be small enough to circulate and bind to cancer cells, thus blocking their ability to adhere to galactose residues on host cell surfaces or the extracellular matrix. The proposed mode of action of MCP is saturation of galactose binding sites of cancer cell lectins, inhibiting both the aggregation of tumor cells and their adherence to normal cells. This effect has been demonstrated by Platt and Raz on lung metastasis using B16-F1 melanoma cells, where MCP almost completely blocked cell aggregation and metastasis.¹¹

Pienta *et al.* used a male Copenhagen rat model to evaluate efficacy of orally administered MCP against metastasis.^{8,10} Rats were injected with rat prostate cancer cells. On Day 4 after injection groups were offered drinking water containing 0.00%, 0.01%, 0.10%, or 1.00% MCP. On day 14 the tumor-bearing hind limbs were amputated under anesthesia and the tumors weighed. The rats were sacrificed at day 30 and the numbers of secondary tumors counted. The authors found orally administered MCP did not affect primary tumor growth in the rats but did inhibit metastases. In the two control groups (0.00% and 0.01% MCP), 15 of 16 rats had lung metastases; the 16th rat had only lymph node metastases. Of the groups of rats receiving 0.10% and 1.0% MCP in their water, approximately half in each group had no metastases. In addition, the 1.0% MCP group had significantly fewer metastases in the lungs ($p<.001$) and lymph nodes ($p<.01$) compared to controls.



Arabinogalactan

Simple sugars like lactose and galactose can block lectins, but small animal patients are generally lactose-intolerant. Lactose and galactose would be too rapidly metabolized for effective binding to lectins on cancer cells. Other sources of lectin-binding polysaccharides include arabinogalactan, isolated from the larch tree.¹⁵ In one study with sarcoma L-1 tumor cells, larch arabinogalactan completely blocked metastases of tumor cells to the liver of Balb/c mice and greatly reduced metastases of ESb lymphoma cells to the liver of DBA/2 mice.¹⁶ Hagmar and others in a 1991 study injected hepatoma cells that primarily colonize the liver to investigate the effects of arabinogalactan treatment against liver metastases. Syngeneic mice treated with arabinogalactan had reduced liver metastases and prolonged survival times compared to controls.¹⁷ Arabinogalactan has also been isolated from medicinal plants that have immune-modulating effects including *Baptisia tinctoria* (wild indigo)¹⁸, *Echinacea purpurea*,^{18,19} *Ginkgo biloba*,²⁰ the berries of *Viscum album* (mistletoe),²¹ raspberry juice,²² *Panax ginseng*,²³ and the medicinal fungi, *Ganoderma lucidum*.²⁴

Unlike conventional chemotherapy agents, these plant-derived polysaccharides may have other beneficial effects for the cancer patient including support for intestinal flora, increased production of short-chain fatty acids from intestinal fermentation, decreased ammoniogenesis, and enhanced macrophage or NK cell activity. For example, arabinogalactan isolated from *Echinacea purpurea* and injected into the peritoneum enhanced macrophage cell cytotoxicity against tumor cells. Purified acidic arabinogalactan treatment induced macrophages to produce tumor necrosis factor (TNF-alpha), interleukin-1 and interferon-beta 2.¹⁹

Clinical application

Animals including humans have consumed pectin and related cell-wall constituents for a long time. The galectins, arabinogalactans, and similar immune-enhancing polysaccharides from soluble plant fiber have inherently low toxicity for animal use. They are components of ordinary foods or have been used medicinally for centuries.

MCP is available commercially as Pecta-Sol (Nu-Biologics, Warrenville, IL). The recommended dose for a human adult is 15 grams daily. Small animals may be dosed at 1 gram for every 10 pounds of body weight, divided into three servings per day. Each teaspoon of powder contains approximately 2.5 grams. The powder should be stirred briskly into water, broth, or other liquid, or can be mixed with moist foods. The professional cost for 454 g. is \$68.95, or roughly \$.15 per gram. A 60-pound dog would require \$.90 of product daily while undergoing cancer therapy.

Situations in which the use of MCP in cancer therapy would be most practical:

1. following early detection of the primary tumor
2. for aggressive neoplasms such as malignant histiocytoma, melanoma, mammary adenocarcinomas, and others
3. as adjunctive therapy following surgical resection of a primary tumor

Summary

Research has demonstrated that MCP inhibits metastasis of tumor cells in the mouse and rat, when few other anti-metastatic therapies are available. As a soluble plant fiber, MCP is unlikely to trigger intolerance, even with long-term consumption. MCP's inherent safety, low cost, and proven activity in blocking metastasis warrant further investigation as an oral therapy in small animal cancer patients.

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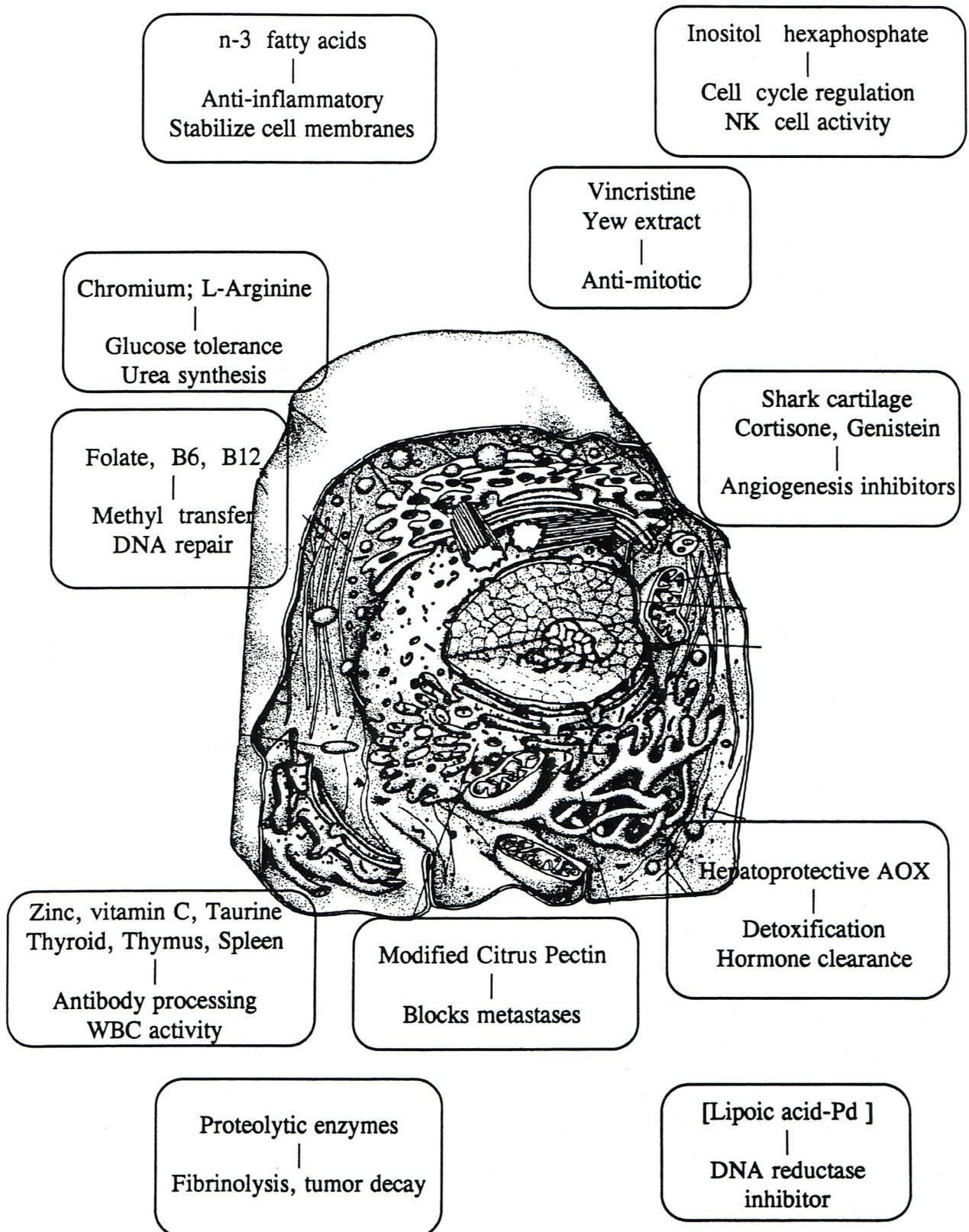
About the speaker

William K. Kruesi, M.S., D.V.M. is the principal veterinarian at Cold River Veterinary Center, North Clarendon, Vermont. His special interests include the application of natural therapies in small animal medicine. Kruesi graduated with honors from Tufts University School of Veterinary Medicine, where he also received the Pathology Award, and Amelia Peabody Award. He holds a Bachelor of Science degree, *Summa cum laude* in Plant Science, and a Master of Science degree in Horticulture from Rutgers University. He completed one year of post graduate education in Animal Science from Cornell University, and pursued continuing education courses in veterinary homeopathy, applied kinesiology and clinical nutrition, feline medicine and surgery, ultrasound imaging, gastroenterology, neurology, and cardiology.

Cold River Veterinary Center is a private practice that emphasizes a holistic approach to animal health. The veterinarian and staff at CRVC offer several types of non-toxic cancer therapies, nutritional analyses, homeopathic remedies, glandular, vitamin, mineral, and herbal supplements.

William Konrad Kruesi's interest in complementary therapies is due largely to the example set by his father, Dr. Oscar Rogers Kruesi, M.D., F.A.C.P. Dr. Oscar Kruesi is Director of New Health Initiatives, a clinical research facility for integrative medicine. This outpatient clinic emphasizes preventive health care using nutritional, conventional and alternative therapies. Dr. Kruesi has been in private practice for 43 years. In addition to his medical practice he is Chairman of the Department of Natural Medicine and Associate Professor of Clinical Medicine at Capitol University of Integrative Medicine, Washington, D.C.

Natural cancer therapy is directed at many points that inhibit tumor growth, metastases, and improve the patient's well being.



Cold River Veterinary Center— *Natural Cancer Therapies*

For:

Recommended ✓

Acemannin: injectable aloe extract	
Aloe vera gel, aloe juice	
Amino acids therapy: L-Arginine; L-Glutamine; L-Ornithine, etc.	
Antioxidant enzymes: superoxide dismutase (Palosein)	
Benefin shark fin cartilage	
Deionized water, intralesional	
Diet and nutritional therapy	
Digestive enzymes: bromelain, papain, etc.	
Dimethyl sulfoxide, topical or IV	
EDTA oral chelation therapy	
Essential fatty acids	
ESSIAC tincture	
Frozen Car-T-Cell shark cartilage	
Frozen thymus extract	
Germanium sesquioxide	
Gland extracts: thyroid, spleen, lymph, etc.	
Homeopathic remedies	
Hydrogen peroxide, intralesional or IV	
Immuno Augmentative Therapy	
Inositol hexaphosphate	
Intravenous vitamin and mineral therapy, detox programs	
Lipoic acid-palladium compound	
Medicinal herbs	
Medicinal mushrooms: Maitake, Shiitake, reishi	
Minerals: Zn, Cu, Fe, Se, Mo, Cr, Si, etc.	
Mitochondrial support: N-Acetyl-Cysteine, ubiquinone, etc.	
Modified citrus pectin	
Natural hydrocortisone	
Physical therapy, massage	
Phytonutrients: anthocyanidins, carotenoids, flavones, bioflavonoids, etc.	
Traditional Chinese Medicines: Milletia, Astragalus, etc.	
Vincristine, cyclophosphamide, hydrocortisone (COP)	
Viscum alba, homeopathic preparation	
Vitamins: A, B, C, D, E, K	
Yew extract	

Cancer: early warning signs from routine chemistry profiles and blood cell counts

1

PARAMETER	REFERENCE RANGE (Canine)	CHANGE ASSOCIATED WITH CANCER	EARLY WARNING THRESHOLD	COMMENTS
Glucose	70 - 138 mg/dl	↓	< 80 mg/dl	Rapidly growing tumors can consume blood glucose, causing episodes of hypoglycemia.
Total protein	5.0 - 7.4 g/dl	↑	> 8.0 g/dl	Elevated serum proteins are associated with dehydration, chronic inflammation, and some malignancies such as myeloma.
ALT AST Alkaline phosphatase	12 - 118 U/L 15 - 66 U/L 5 - 131 U/L	↑	> 250 U/L > 66 U/L > 450 U/L	Each of these enzyme activities may relate to liver inflammation, reduced bile outflow, or necrosis (cell injury and death). Markedly elevated ALT, AST, and/or Alkaline phosphatase activity should be pursued to determine the cause of the abnormal value.
GGTP	1 - 12 U/L	↑	> 6	Gamma-Glutamyltransferase (GGTP) is a more specific marker for inflammation of the biliary system (gall bladder and bile ducts) than alkaline phosphatase. Elevations in GGTP are nearly always associated with injury or leakage of epithelial cell membranes that line the bile ducts. Marked elevations, i.e. 30-100 U/L may be associated with a mass that obstructs bile flow or is invasive.
Calcium	8.9 - 11.4 mg/dl	↑ OR ↓	< 8.5 or > 12	The body under normal conditions closely regulates serum calcium concentration. Certain adenocarcinomas, and lymphomas are associated with a paraneoplastic syndrome of hypercalcemia. Dogs and cats with bone destroying tumors or liver cancer may have very low serum calcium.

Note: this information should not be interpreted as a method to diagnose or treat cancer in dogs or cats. It is intended to be a starting point for the clinician to pursue a definitive diagnosis, once abnormal values are observed on routine serum chemistry tests and blood cell counts. The values identified as "early warning threshold" are from my experience, in diagnosing and treating veterinary patients.

Cancer: early warning signs from routine chemistry profiles and blood cell counts

2

PARAMETER	REFERENCE RANGE (Canine)	CHANGE ASSOCIATED WITH CANCER	EARLY WARNING THRESHOLD	COMMENTS
Phosphorus	2.5 – 6.0 mg/dl	↓	< 2.5 mg/dl	Phosphorus is released from food through the action of acid in the stomach, and absorbed in the small intestine. In small animals with normal appetite, a low phosphorus level implies a state of hypochlorhydria (low gastric acid secretion), or more commonly, poor absorption through the small intestine. Low phosphorus is often seen in patients with alimentary lymphoma or inflammatory bowel disease.
Chloride	102 – 120 mEq/L	↓	< 98 mEq/L	Chloride is secreted into the stomach as hydrochloric acid. It is also a common ingredient in pet food, as salt (sodium chloride). Chloride flows out of the stomach and is absorbed in the small intestine. It is also absorbed or conserved by the kidneys. Low chloride is suggestive of hypochlorhydria, or more commonly, poor absorption through the small intestine. Low chloride (and/or low phosphorus) is seen in patients with alimentary lymphoma or inflammatory bowel disease.
Cholesterol	92 – 324 mg/dl	↓	< 120	Cancer cells do not have the metabolic means to synthesize cholesterol; instead they consume serum cholesterol and can cause a marked depletion even in patients with sufficient food intake. Patients with moderately low cholesterol, i.e., <145 mg/dl may be under significant oxidative stress, and may benefit from therapeutic levels of antioxidant enzymes, vitamins, and minerals, as well as nutritional support for the liver.

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Cancer: early warning signs from routine chemistry profiles and blood cell counts

3

PARAMETER	REFERENCE RANGE (Canine)	CHANGE ASSOCIATED WITH CANCER	EARLY WARNING THRESHOLD	COMMENTS
Globulin	1.6 – 3.6 g/dl	↑	> 4.5 g/dl	Immunoglobulins (antibodies) are normally not produced in excess. Very high levels are suggestive of a gammopathy or primary disorder of plasma cells (specialized B-lymphocytes), i.e., plasma cell tumor or myeloma. Other causes of high globulin levels include dehydration (hemoccentration), tick-borne diseases, and perhaps vaccination.
Basophils	0 – 150 cells/cmm	↑	> 80 cells/cmm	Basophils in the circulation are rare. Their presence should alert the clinician to be wary of mast cell tumor or melanoma. Basophils are also associated with hypertriglyceridemia, heartworm disease, and some parasite infections.
Eosinophils	0 – 1200 cells/cmm	↑	> 1200 cells/cmm	Eosinophilia is associated with mast cell tumors, lymphoma, and neurofibroma (nerve sheath tumors). High numbers of eosinophils are also seen with myocardial infarcts, flea allergy, or asthma.
Lymphocytes	690 – 4500 cells/cmm	↓	< 690 cells/cmm	The number and proportion of lymphocytes often increases with chronic inflammation or persistent viral infections. Low absolute numbers of lymphocytes (lymphopenia) is seen with lymphoma, leukemia, and other immune suppressive diseases.
Thyroxine (T4)	1.0 – 4.0 mcg/dl	↑ OR ↓	< 1.0 or > 4.5 mcg/dl	Small animals with infection or suffering from tumor necrosis syndrome may have severely depressed thyroid hormone levels. All of the thyroid hormones, e.g., T3, T4, and fT4 will tend to be low. On the other extreme, animals with thyroid adenomas or thyroid carcinomas may have persistent hyperthyroidism. Always interpret thyroid levels with an accurate history of medications taken.

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PARAMETER	REFERENCE RANGE (Canine)	CHANGE ASSOCIATED WITH CANCER	EARLY WARNING THRESHOLD	COMMENTS
Potassium	3.6 – 5.5 mEq/L	<div> <div>↑</div> <div>OR</div> <div>↓</div> </div>	< 4.0 or > 5.0 mEq/L	Abnormally low or high serum potassium with low or high creatine phosphokinase (CPK, CK) are suggestive of cardiac muscle injury. CPK is found primarily in skeletal and cardiac muscle; high serum concentrations are associated with muscle injury or trauma. The right atrial appendage is a common site of hemangiosarcoma. This and other heart base tumors (and non-cancerous heart disease) can destroy cardiac muscle causing abnormal potassium and CPK values.
Creatine phosphokinase (CPK)	59 – 895 U/L	<div> <div>↑</div> <div>OR</div> <div>↓</div> </div>	< 100 or > 300 U/L	

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